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Patent Administrator
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| EXAMINER | |
|---|---|
| ANGELL, JON E | |
| **ART UNIT** | **PAPER NUMBER** |
| 1635 | 16 |

DATE MAILED: 10/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/763,682 | BJERKVIG, ROLF | |
| | Examiner | Art Unit | |
| | J. Eric Angell | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *12,14-21,24-28,30 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,14-21,24-28,30 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6, 12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. This Action is in response to the communication filed on 7/10/03, as Paper No. 14. The amendment has been entered. Claims 12, 14-21, 24-28, 30 and 32 are currently pending in the application and are examined herein.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

### *Claim Rejections - 35 USC § 112*

The rejection of claims under 35 USC 112 first and second paragraphs have been withdrawn in view of the amendment to the claims and/or applicants arguments.

### *Claim Rejections - 35 USC § 103*

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 12, 14-21, 24-28, 30 and 32 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Aebischer (WO 97/38707 A1, 1997) in view of O'Reilly (US Patent 5,854,205, filed 10-22/1996) and further in view of Skjak-Braek (U.S. Patent 5,459,054; 1995), for the reasons of record, which were previously set forth and are reiterated below.

Aebischer teaches composition comprising a producer cell that expresses a molecule (here FasL) that can be used as a treatment to inhibit CNS tumor growth (see p. 2-3) wherein the cell is encapsulated to protect the cell from the host's immune response (see p. 14).

Aebischer does not teach that the molecule is endostatin.

Aebischer does not teach that the encapsulating matrix is made up of immunoisolating alginate having a G content of above 15%, that the therapeutic molecule affects tumor neovascularization, that the producer cell is present in a bead or a microbead, or the therapeutic molecule produced by the encapsulated cell is endostatin.

O'Reilly (US Patent) teaches that endostatin is a polypeptide which can inhibit cell proliferation and angiogenesis (see abstract). O'Reilly teaches that nucleic acid encoding endostatin can be used to modulate endothelial processes in vivo and to treat disease by gene therapy (see column 9, lines 29-45). O'Reilly indicates that nucleic acid sequence corresponding to the amino acid sequence could be prepared by one of ordinary skill in the art based upon the amino acid sequence (see column 9, lines 39-45). O'Reilly teaches that endostatin protein and the nucleic acid encoding endostatin can be used to treat a number of different diseases, including solid tumors (see column 4, lines 4-19), and specifically tumor metastases, including acoustic neuromas, neurofibromas, etc. (see column 10, lines 33-60) which includes tumors of the CNS and brain.

Skjak-Braek et al. teaches a composition comprising a producer cell which does not express a molecule that inhibits tumor growth, but is an encapsulated cell wherein the producer cell is encapsulated in a matrix that comprises an immunoisolating alginate having a G content of above 15%, above 50%, 60-80%, and 80-100%, wherein the producer cell is encapsulated in a

bead, wherein the alginate is substantially pure of endotoxin, (see abstract; col. 4, lines 44-67; col. 7, lines 15-18; and Example 7). Skjak-Braek et al. also teaches that the encapsulated cells are living cells (col. 4, lines 7-11) which are naturally occurring or genetically engineered prokaryotic or eukaryotic cells (see col. 4, lines 53-57), and that the encapsulated cells "can be implanted or transplanted in vivo into mammals without inducing any substantial immunogenic reaction or fibroblast formation" and can be used "as a drug or biological material delivery system." (See col. 4 lines 44-58).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the composition taught by Aebischer such that 1) the cell expresses endostatin and 2) the immunoisolating alginate taught by Skjak-Braek is substituted for the encapsulating matrix of Aebischer, with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to create an encapsulated producer cell for treatment of a brain/CNS tumor by substituting the nucleic acid encoding endostatin for the nucleic acid encoding FasL in the producer cell, because 1) both molecules were known in the art as cancer therapeutic molecules, and 2) specifically, because O'Reilly teaches that the nucleic acid encoding endostatin could be used to treat solid tumors and tumor metastases including acoustic neuromas, neurofibromas. Furthermore, one of ordinary skill in the art would have been motivated to encapsulate the producer cell indicated above (in view of Aebischer and O'Reilly) with the immunostimulating alginate taught by Skjak-Braek because Skjak-Braek teaches that the alginate with a high concentration of G and low concentration of M has a reduced immunostimulatory effect when transplanted into a mammal, which protects the cell from the mammal's immune response and fibroblast formation better than an alginate with a

high concentration of M and a low concentration of G (such as in Aebischer) (see columns 1-3 and column 4, lines 44-66; column 6, lines 33-54).

***Response to Arguments***

5. Applicant's arguments filed 7/10/03 have been fully considered but they are not persuasive.

6. Applicants' first point out that claim 12 has been amended to indicate that the composition is an inhibitor of the growth of a ***malignant*** CNS tumor (see p. 11 of response). Applicants contend that the Office fails to identify any credible evidence of motivation, teaching or suggestion that would have led persons of ordinary skill in the art to combine the teachings the art of record (see p. 11 of response). Additionally, Applicants argue that O'Reilly fails to teach, disclose or suggest that endostatin is an inhibitor of the growth of malignant CNS tumors.

7. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

8. In response to Applicants arguments that O'Reilly does not teach that endostatin could be used to treat malignant CNS tumors, the Examiner respectfully disagrees. Considering the teaching of O'Reilly in whole, O'Reilly specifically indicates that endostatin can be used to treat "endothelial cell-related diseases and disorders" including angiogenesis-related disorders (see

column 10, lines 33-35). Furthermore, O'Reilly teaches "Angiogenesis-related diseases include, but are not limited to, angiogenesis-dependent cancer, including, for example, solid tumors blood born tumors such as leukemias, and tumor metastases" (see column 10, lines 40-45). Even if, for arguments sake only, O'Reilly does not explicitly teach that endostatin could be used to treat malignant CNS tumors, that fact that O'Reilly does indicate that endostatin can be used to treat angiogenesis-dependent cancer, including, solid tumors blood and tumor metastases would have made it obvious to one of ordinary skill in the art that endostatin could be used to treat malignant CNS tumors.

9. In response to applicant's argument that there is no suggestion/motivation to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) And *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one of ordinary skill in the art would have been motivated to create an encapsulated producer cell for treatment of a brain/CNS tumor by substituting the nucleic acid encoding endostatin for the nucleic acid encoding FasL in the producer cell, because 1) both molecules were known in the art as cancer therapeutic molecules, and 2) specifically, because O'Reilly teaches that the nucleic acid encoding endostatin could be used to treat solid tumors and tumor metastases including (but not limited to) acoustic neuromas, neurofibromas. It is pointed out that O'Reilly indicates that endostatin is useful for treating angiogenesis-related cancers including tumor metastases (see column 10, lines 40-45), which certainly encompasses

malignant tumors. Even if, for arguments sake only, that O'Reilly doesn't explicitly teach that endostatin could be used to treat malignant CNS tumors, it would have been obvious to the skilled artisan that endostatin could be used to treat malignant CNS tumors, based on the teachings of O'Reilly discussed herein.

10. It is also respectfully pointed out to the Applicants that claims 19, 21, 27, 28 and 30 are not specifically limited to compositions and methods of treatment useful for treating malignant CNS tumors, but encompass composition/method for treating any CNS tumor.

11. For the reasons set forth above, applicants' arguments are not persuasive and the instant claims stand rejected under 35 USC 103.

***Conclusion***

No claim is allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell

DAVE T. NGUYEN
PRIMARY EXAMINER